

**WHAT IS CLAIMED IS:**

1        1.    A small interfering RNA (siRNA) comprising at least one modified base, wherein  
2        the modified base is capable of enhancing single nucleotide discrimination between a first  
3        target having 1, 2, 3 or more mutations relative to a second target.

4  
5        2.    A small interfering RNA (siRNA) capable of single nucleotide discrimination  
6        between a first and second allele, the first allele having 1, 2, 3 or more mutations relative  
7        to the second allele, wherein the siRNA comprises at least one modified base capable of  
8        enhancing binding interactions between the siRNA and mRNA encoded by the first allele  
9        when compared with binding interactions between the siRNA and mRNA encoded by the  
10       second allele.

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12       3.    A small interfering RNA (siRNA) comprising a sense strand and an antisense  
13       strand, wherein the sense strand comprises a sequence homologous to a region of a  
14       mutant allele encoding a gain-of-function mutant protein, said region comprising one or  
15       more point mutations, and wherein the antisense strand comprises a sequence comprising  
16       one or more modified bases positioned opposite the point mutations, such that the siRNA  
17       directs allele-specific cleavage of a mRNA encoded by the mutant allele.

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19       4.    The siRNA of any one of claims 1-3, wherein the modified base is selected from the  
20       group consisting of 5-bromo-uridine, 5-bromo-cytidine, 5-iodo-uridine, 5-iodo-cytidine,  
21       2-amino-purine, 2-amino-allyl-purine, 6-amino-purine, 6-amino-allyl-purine, 2, 6-  
22       diaminopurine and 6-amino-8-bromo-purine.

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24       5.    The siRNA of claim 4, wherein the modified base is 5-bromo-uridine or 5-iodo-  
25       uridine.

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27       6.    The siRNA of claim 5, wherein the point mutation is an adenine.

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29       7.    The siRNA of claim 4, wherein the modified base is 2,6-diaminopurine.

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- 31 8. The siRNA of claim 7, wherein the point mutation is a thymine.
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- 33 9. The siRNAi of claim 3, which targets an allelic point mutation within a gene
- 34 correlated with a disorder selected from the group consisting of amyotrophic lateral
- 35 sclerosis, Huntington's disease, Alzheimer's disease, and Parkinson's disease.
- 36
- 37 10. The siRNA of any one of claims 1-3, which is between about 10 and 50 residues in
- 38 length.
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- 40 11. The siRNA of any one of claims 1-3, which is between about 15 and 45 residues in
- 41 length.
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- 43 12. The siRNA of any one of claims 1-3, which is between about 20 and 40 residues in
- 44 length.
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- 46 13. The siRNA of any one of claims 1-3, which is between about 18-25 residues in
- 47 length.
- 48
- 49 14. A therapeutic composition, comprising the siRNA of any one of claims 1-3 and a
- 50 pharmaceutically acceptable carrier.
- 51
- 52 15. A host cell comprising the siRNAi of any one claims 1-3.
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- 54 16. The host cell of claim 15, which is mammalian cell.
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- 56 17. The host cell of claim 15, which is a human cell.
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- 58 18. A method of selectively targeting in a cell a first allele having 1, 2, 3 or more
- mutations relative to a second allele, the method comprising contacting the cell with an
- siRNA according to any one of claims 1-3 having a sequence specific for the first allele,
- such that the first allele is selectively targeted.

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60 19. A method of inhibiting expression of a target allele in a cell comprising at least two  
61 different alleles of a gene, the method comprising introducing into the cell an siRNA  
62 according to any one of claims 1-3 having a sequence specific for the target allele, said  
63 siRNA being introduced in an amount sufficient for degradation of a mRNA encoded by  
64 the target allele to occur, thereby inhibiting expression of the target allele.

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66 20. The method of claim 19, wherein the target allele is correlated with a disease or  
67 disorder associated with a dominant gain-of-function mutation.

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69 21. The method of claim 20, wherein the disease or disorder is chosen from the group  
70 consisting of amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease,  
71 and Parkinson's disease.

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73 22. The method of claim 19, wherein the expression is inhibited by at least 10%.

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75 23. A cell obtained by the methods of claim 19.

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77 24. A cell of claim 23, which is of mammalian origin.

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79 25. A cell of claim 24, which is of human origin.

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81 26. A cell of claim 24, which is an embryonic stem cell.

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83 27. A method of activating allele-specific RNA interference (RNAi) in an organism  
84 comprising at least two different alleles of a gene, the method comprising administering  
85 to the organism the siRNA of any one of claims 1-3 having a sequence specific for the  
86 target allele, said siRNA being administered in an amount sufficient for degradation of  
87 the target allele mRNA to occur, thereby activating allele-specific RNAi in the organism.

89        28. The method of claim 27, wherein the target allele is correlated with a disease or  
90 disorder associated with a dominant gain-of-function mutation.

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92        29. The method of claim 28, wherein the disease or disorder is chosen from the group  
93 consisting of amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease,  
94 and Parkinson's disease.

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96        30. The organism obtained by the method of claim 27.

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98        31. A method of treating a subject having a disease or disorder correlated with the  
99 presence of a dominant gain-of-function mutant allele, the method comprising  
100 administering to the subject an siRNA of any one of claims 1-3 having a sequence  
101 specific for the mutant allele, said siRNA being administered in an amount sufficient for  
102 degradation of a mRNA encoded by the mutant allele to occur, thereby treating the  
103 subject.

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105        32. The method of claim 31, wherein the disease or disorder is chosen from the group  
106 consisting of amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease,  
107 and Parkinson's disease.

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109        33. The method of claim 31, wherein the siRNA is targeted to the gain-of-function  
110 mutation.

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112        34. The method of claim 31, wherein the mutant allele comprises one or more point  
113 mutations.